Topic 8 – Oxydative stress, NO, ageing – B

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0330

Fixed ranking of leukocyte telomere length in elderly people: results from 8 year follow-up of the ADELAHYDE cohort

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Introduction: Short leukocyte telomere length (LTL) is associated with atherosclerosis in adults and diminished survival in the elderly. The prevailing view is that LTL is associated with accelerated aging since it serves as a biomarker of the cumulative burden of inflammation and oxidative stress during adult life. LTL dynamics are defined by LTL at birth, which is highly variable, and its age-dependent attrition thereafter, which is rapid during the first 20 years of life. We examined whether age-dependent LTL attrition during old age can substantially affect individuals' LTL ranking (e.g., longer or shorter LTL) in relation to their peers and which clinical, lifestyle or genetic factors can predict it.

Methods: We measured LTL by Telomeric Restriction Fragment Southern Blot (TRF) in samples donated 8 years apart on average by 76 participants of the ADELAHYDE study. Participants were men and women aged 60 to 85 years with a history of hypertension at the inclusion.

Results: We observed a mean LTL attrition of 27 bp per year which is consistent with previous data on telomere attrition in adults. No clinical, lifestyle or genetic factors seem to exert significant effect or can predict LTL attrition in elderly people. We observed a close relationship (r=0.88, figure left panel) between baseline and follow-up LTL values. Ranking individuals by quintiles revealed that 98.6 % showed no rank change (59.7%) or one quintile change (38.9%) over time (figure right panel).

Conclusions: We conclude that in elderly people, LTL is virtually anchored to a given rank with the passage of time. Accordingly, the links of LTL with atherosclerosis and longevity appear to be established early in life. It is therefore unlikely that lifestyle and its modification during old age exert a major impact on LTL ranking.

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Role of Sirtuin 3 in cardioprotection – evolution with aging

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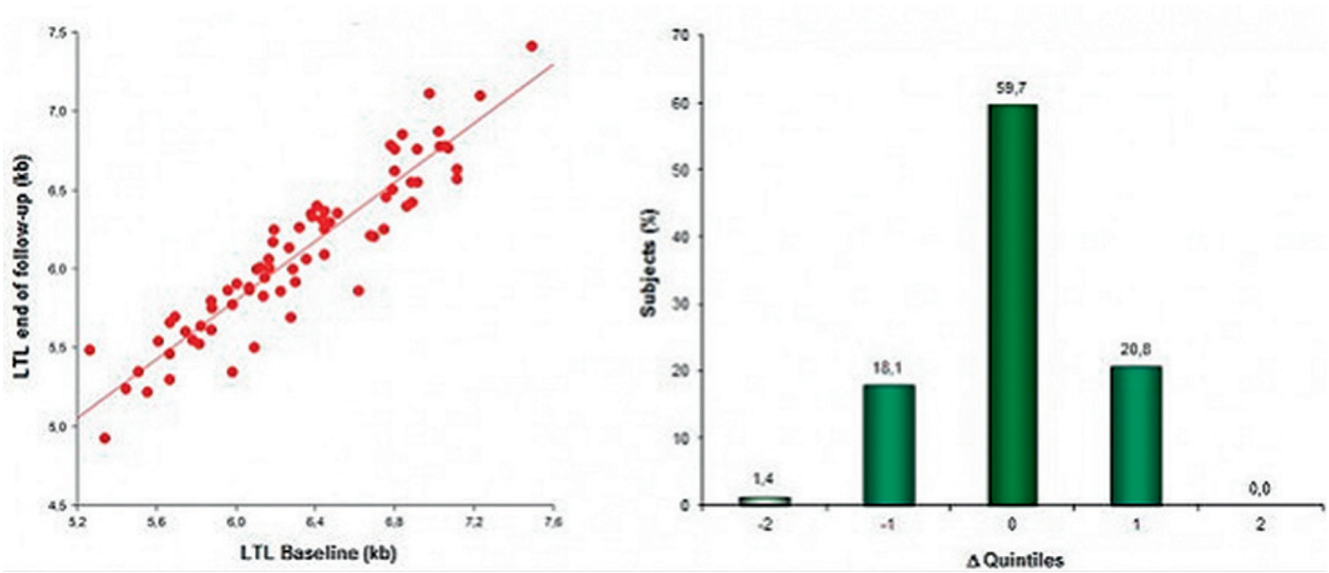
Mitochondrial dysfunction contributes to the pathogenesis of a wide variety of common diseases, including cardiovascular diseases. Mitochondria-triggered cell death is a major cause of cardiac injury following ischemia reperfusion (I/R). Aging is a physiological evolution of organisms and the concept that mitochondrial function declines during aging has been largely described for many years. Furthermore, aging is a major risk factor for myocardial infarction. Sirtuin 3 (SIRT3) is a member of Sirtuin family which is a NAD+ dependent deacetylase, preferentially localized into mitochondria. SIRT3 deacetylates some of the regulatory components of the mitochondrial permeability transition pore (mPTP), cyclophilin D (CypD) and complexes of the electron transport chain, both known to be involved in cardioprotection. The goal of this study was to clarify the role of SIRT3 in cardioprotection following aging, and its mechanism of action through mitochondrial functions.

To do so, we used WT and Sirt3 KO mice (129S6/SvEvTac) at different ages: 2, 6 and 12 months. Mice underwent in vivo acute myocardial ischemia-reperfusion at different ages. The infarct size was quantified and compared between the different ages. Total mitochondrial acetylation, and acetylation level of CypD and Complex I were quantified and in parallel we assessed mPTP sensitivity to Ca2+ using Calcium Retention Capacity and Oxidative Phosphorylation.

Our results show that the absence of SIRT3 prevents the beneficial effect of cardioprotection by ischemic post-conditioning. SIRT3 KO mostly changes the acetylation status of CypD and Complex I, and also increases by almost 30% mPTP sensitivity to Ca2+. We also demonstrate that aging changes SIRT3 activity, which increases protein acetylation and decreases mPTP sensitivity to Ca2+.

Globally, this study enlightens the importance of SIRT3 activity as a therapeutic target in cardioprotection.



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